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Alendronate-induced esophagitis

Alendronate sodium (Fosamax®), an aminobisphosphonate, is an inhibitor of bone resorption approved for use in Canada for the treatment of Paget's disease and for the prevention and treatment of postmenopausal osteoporosis.

From December 1995, when Fosamax® was approved for sale in Canada, to January 1998 the Canadian Adverse Drug Reaction Monitoring Program (CADRMP) received 138 reports, of which 78 were suspected gastrointestinal reactions associated with the drug. Fourteen reports described esophageal reactions: esophagitis (9), esophageal ulceration (3), esophageal stricture (1) and esophageal perforation (1). In the last case the perforation was later shown to have occurred during surgery and was not considered related to the alendronate therapy. The cases of ulceration and stricture are described here.

Case 1: A 62-year-old woman had received an unknown dose of alendronate for an unknown duration to treat her osteoporosis. The reporter indicated that the patient required hosp talization. She had coffee-ground emesis and became acidotic. Endoscopy revealed a severe gastroesophageal erosion and evidence of alendronate tablets still adhering to the esophageal wall. Treatment included ranitidine given intravenously for 3 days followed by omeprazole (20 mg twice daily). The patient recovered. It is unknown whether the patient had adhered to the instructions for taking the alendronate. The only concomitant medication was insulin.

Case 2: A 64-year-old woman received 10 mg of alendronate daily for 4 weeks. Three weeks after initiation of the therapy she was admitted to hospital with an acute exacerbation of rheumatoid arthritis. After admission the patient began to complain of nausea, vomiting and epigastric pain. Laboratory results showed a drop in the hemoglobin level, from 123 (normally 115-155) g/L on the day after admission to 102 g/L 5 days later. An esophageal ulcer was confirmed by gastroscopy 9 days after admission. The ulcer was treated with omeprazole (20 mg/d). At the time of reporting, 1 week later, the patient had not yet recovered. Concomitant medications of several months' duration included prednisone (7.5 mg/d), halibut liver oil (1 capsule/d), calcium (1500 mg/d) and acetaminophen (as required for pain). One month after the reaction, follow-up confirmed that the alendronate had not been taken with enough water.

Case 3: An 82-year-old woman who was an inpatient in a behavioural stabilization unit received an unknown dose of alendronate. Details of how the alendronate was administered were not provided in the report. After 6 weeks of therapy the hemoglobin level dropped to 86 g/L. Endoscopy revealed 2 erosions of the esophagus below 20 cm. The patient recovered after discontinuation of the alendronate therapy and treatment with omeprazole (40 mg/d for 1 month). She had a history of alcohol abuse and was receiving other medications, none of which was known to be associated with the development of gastrointestinal disorders.

Case 4: A 77-year-old woman received 10 mg of alendronate daily for at least 2 months. Results of a barium swallow showed an esophageal stricture. The reaction was discovered while the patient was in hospital and resulted in prolongation of her stay. The patient's outcome was not reported. She was reported not to have taken the alendronate in a sitting position or with sufficient water.

The mechanism of esophageal injury with alendronate has not been determined but may be due to failure of the tablet to pass through the esophagus, resulting in prolonged mucosal exposure to the drug. As well, reflux of drug-containing gastric contents may be part of the pathophysiology.<1> A recent randomized, crossover,

placebo-controlled study comparing the mucosal damage caused by alendronate (40 mg), ASA (1300 mg) and placebo in 12 healthy subjects showed gastric mucosal injury, visible on endoscopy, in 58%, 75% and 0% of the subjects respectively. The damage in the 2 drug groups was significantly greater than that in the placebo group ($p < 0.001$) and was rated as severe (3 or more areas of erosion or large areas of erosion with widespread involvement of the mucosa or ulcer) in half of the patients taking either alendronate or ASA. The authors concluded that alendronate causes mucosal injury to the upper gastrointestinal tract similar to that caused by ASA.<2>

In premarketing studies adverse esophageal effects occurred in 15% to 18% of patients receiving either placebo or alendronate (doses of 5, 10 and 40 mg) and were considered serious or severe in 1.5% of all patients in all 4 treatment groups.<3> However, postmarketing experience has shown that a greater proportion of esophageal reactions are reported as serious. A 1996 review of postmarketing data summarized that 199 esophageal-related adverse reactions had been reported worldwide among 470 000 patients.<1,3> Of these 199 cases, 51 were considered severe and 32 required admission to hospital. This difference in frequency of serious reactions between the pre- and postmarketing experiences may be explained by the frequent follow-up visits and reinforcement of dose instructions that participants in the premarketing studies would have received.<1,3>

Several case reports have been published documenting esophageal injury with alendronate therapy. In the majority of cases patients were not compliant with the instructions for administration.<1,4-6> Esophageal injury has been reported in patients who did comply with instructions but who had a history of esophageal disorders<1,7> and in patients with no apparent risk factors other than increased age.<1> Some clinicians have suggested that esophageal injury can still occur despite adherence to dosing guidelines and have recommended that patients be monitored regularly and on a long-term basis for compliance and adverse effects.<8>

The current recommendations for alendronate administration given in the product monograph are intended to facilitate delivery to the stomach and thus reduce the potential for esophageal irritation:

- The tablet should be swallowed with a full glass of water (200-250 mL) at least 30 minutes before the first food of the day.
- The patient should remain upright for at least 30 minutes after taking the tablet *and* after the first food of the day.
- Worldwide, the labelling for Fosamax® has been revised: the contraindications have been expanded to include patients who have esophageal abnormalities that result in delayed emptying

(e.g., stricture or achalasia) and those who are unable to stand or sit upright for at least 30 minutes.

- Patients should be instructed to stop therapy if they experience any symptoms of esophageal problems (difficulty or pain upon swallowing, retrosternal pain, or new or worsening heartburn) and to consult their physician immediately.

This article is under the direction of: Lynn Macdonald, BSP, Bureau of Drug Surveillance.

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Adverse drug reaction reporting – 1997

The sources of reports of adverse drug reactions (ADRs) submitted to the CADRMP remained virtually the same as in 1996 (Table 1). In most cases the people who initiate the reports are health professionals (physicians, pharmacists, nurses, dentists, coroners and others) who *suspect* that a drug has played a role in the adverse reaction and who voluntarily complete an ADR reporting form and forward it directly to the CADRMP or indirectly through one of the other sources. The CADRMP would like to thank all of you who reported ADRs for your important contribution to monitoring the safety of drugs in Canada and to encourage you to continue your efforts.

This article is under the direction of: Claire-Marie Wray, PhD, Bureau of Drug Surveillance.

Table 1: Source of reports of adverse drug reactions in Canada in 1996 and 1997

	No. (and %) of reports received			
Source	In 1996		In 1997	
Manufacturer	1659	(39.5)	1549	(38.7)
Regional centre	1052	(25.1)	993	(24.8)
Hospital	730	(17.4)	671	(16.7)
Pharmacist	293	(7.0)	404	(10.1)
Physician	212	(5.0)	151	(3.8)
Other*	252	(6.0)	238	(5.9)
Total	4198	(100.0)	4006	(100.0)

*Includes, but not limited to, professional associations, nursing homes, Health Protection Branch regional inspectors, coroners, nurses, dentists and patients.

COMMUNIQUÉ

The purpose of this section is to increase awareness of recently reported ADRs. The following cases have been selected on the basis of their seriousness, or the fact that the reactions do not appear in the product monograph. They are intended to prompt reporting.

Dorzolamide hydrochloride (Trusopt®)

Dorzolamide, a topical carbonic anhydrase inhibitor, is used to treat elevated intraocular pressure. Since first marketed in December 1996, the CADRMP has received 24 reports of suspected ADRs associated with this drug. Of these, 17 reports described 25 adverse effects not consistent with the product information or labelling and involved 8 women, 3 men and 6 patients of unknown sex, aged between 60 and 92 years. The unexpected reactions classified by system organ class include:

- *Cardiovascular disorders:* arrhythmia and chest pressure sensation (1 case); hypertension (2); aggravated hypertension (1); palpitation (1); noninflammatory swelling (1)
- *Gastrointestinal disorders*: severe heartburn (1)
- *Visual and hearing disorders and psychiatric disorders:* anxiety, disorientation, auditory and visual hallucination (1); blindness (2); corneal edema (1); foreign body sensation (2); uveitis and posterior synechiae (1)
- *Body as a whole*: epistaxis (1); nasal congestion (1)
- *Central and peripheral nervous system disorders*: epileptic absence and petit mal (1)
- *Skin disorders*: alopecia (1); urticaria (1)

Hydroxychloroquine sulfate (Plaquenil®)

Hydroxychloroquine, indicated for suppressive treatment and treatment of acute attacks of malaria, is also indicated for the treatment of discoid and systemic lupus erythematosus and of rheumatoid arthritis in patients who have not responded satisfactorily to drugs with less potential for serious side effects. With the increased use of the drug in connective tissue diseases, recent concerns have arisen regarding hydroxychloroquine's retinal toxic effects.

In 1997 the CADRMP received a report involving a 7-year-old girl who had been treated for polyarthropathy for 3 or 4 years. In April 1997 she experienced retinopathy, scotoma, circular ring, macular dysfunction and macular toxic effects. At the time of reporting, 6 months later, the patient had not yet recovered.

Atorvastatin calcium (Lipitor™)

Within 1 or 2 days after starting therapy with atorvastatin (10 mg/d) for elevated cholesterol levels, a 67-year-old man complained that he "did not feel right"; a rash developed shortly afterward. A week later he had shortness of breath and increased weakness. On admission to hospital 3 weeks after the start of atorvastatin therapy he had a petechial rash and ecchymosis. The hemoglobin level was 55 (normally 140-180) g/L, the platelet count 7 (normally 130-400) × 10^9/L and the erythrocyte count 1.48 (normally 4.4-5.8) × 10^{12}/L. The blood counts had been normal 4 months earlier. Bone marrow biopsy revealed aplastic anemia. The atorvastatin therapy was stopped; 6 days later the hemoglobin level was 109 g/L, the platelet count was 60 × 10^9/L, and the erythrocyte count was 3.35 × 10^{12}/L. The outcome of the patient was unknown at the time of reporting. Concomitant medications included levothyroxine, furosemide, nifedipine and metoprolol, all of which he had taken for more than 5 years; lovastatin was taken for several years up until the start of the atorvastatin therapy.

Risperidone (Risperdal™)

A 17-year-old mentally challenged young woman experienced an increase in carbamazepine serum levels after the start of therapy with the antipsychotic drug risperidone (1 mg twice daily). She had been taking carbamazepine (1400 mg/d) for 5 years and had good seizure control. Her carbamazepine level 2 weeks before the start of the risperidone therapy was 49 (normal therapeutic range 16-50) μmol/L. One week after starting risperidone the patient was vomiting, had multiple seizures, was irritable and was lethargic between seizures. She was admitted to hospital 3 days later. Pneumonia was diagnosed, and a toxic carbamazepine level of 105 μmol/L was detected. The risperidone was stopped and the carbamazepine withheld. Four days later the patient's carbamazepine level was 26 μmol/L, and the carbamazepine therapy was restarted. The possibility of an overdose with carbamazepine was ruled out.

Venlafaxine hydrochloride (Effexor®)

Vasospastic (Prinzmetal's) angina developed in a 23-year-old man 8 days after the start of therapy with venlafaxine (37.5 mg twice daily) for depression. The patient had 2 episodes of central and crushing chest pain. The first, occurring 8 days after the start of treatment, woke him in the night and lasted about 45 minutes. The second occurred 2 days later in the early morning and lasted 9½ hours. An electrocardiogram (ECG) in the emergency department

showed 1 mm elevation of the J junction in lead 2 and 3, and atrioventricular fibrillation with flattening of the ascent of the T wave in lead 3 only. A second ECG 4 hours later showed 0.5 mm elevation of the ST segment in lead 3, with very slight convexity of the ST segment of a flat T wave. The total creatine kinase (CK) level was 259 (normally 20-235) U/L, the CK MB (myocardial component) was 29 (normally 0-5) UG/L, and the CK MB relative index was 11 (normally 0-4), which is consistent with myocardial ischemic injury. On both occasions the pain subsided spontaneously. Nontransmural myocardial infarction of the inferior wall was diagnosed, and the patient was admitted to the cardiac care unit. On admission, an echocardiogram was normal. Angiography done the following day showed minor coronary artery disease in the right coronary artery, and a left ventriculogram showed mild inferobasal hypokinesis. The venlafaxine therapy was stopped 3 days after admission. At the time of the report the patient was asymptomatic. He was considered to have virtually no risk factors for heart disease and exercised regularly.

This section is under the direction of: Amal Hélal, BSc Phm, in collaboration with Lynn Macdonald, BSP, and Pascale Springuel, BPharm, Bureau of Drug Surveillance.

This newsletter can be found on line, under Publications, at the following address:
www.hc-sc.gc.ca/hpb-dgps/therapeut

Spontaneous reporting of suspected adverse drug reactions (ADRs) is a critical ongoing source of drug-safety information. Thus, we encourage health professionals to report any suspected ADRs to one of the following addresses:

British Columbia
BC Regional ADR Centre
c/o BC Drug and Poison Information Centre
1081 Burrard St.
Vancouver BC V6Z 1Y6
tel 604 631-5625
fax 604 631-5262

Saskatchewan
Sask ADR Regional Centre
Dial Access Drug Information Service
College of Pharmacy and Nutrition
University of Saskatchewan
Saskatoon SK S7N 5C9
tel 306 966-6340 or 800 667-3425
fax 306 966-6377

Québec
Québec Regional ADR Centre
Drug Information Centre
Hôpital du Sacré Coeur de Montréal
5400, boul. Gouin ouest
Montréal QC H4J 1C5
tel 514 338-2961 or 338-2161
(collect calls accepted)
fax 514 338-3670

New Brunswick, Nova Scotia, Prince Edward Island and Newfoundland
Atlantic Regional ADR Centre
Queen Elizabeth II Health Sciences Centre
New Halifax Infirmary Building
Level 200, Drug Information Centre
1796 Summer St.
Halifax NS B3H 3A7
tel 902 473-7171
fax 902 473-8612

Elsewhere in Canada
Adverse Drug Reaction Reporting Unit
Continuing Assessment Division
Bureau of Drug Surveillance
Therapeutic Products Programme
AL 4103B1
Ottawa ON K1A 1B9
tel 613 957-0337
fax 613 957-0335

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Please Note: A voluntary reporting system thrives on intuition, lateral thinking and openmindedness. For these reasons, most adverse drug reactions (ADRs) can be considered only to be suspicions, for which a proven causal association has not been established. Because there is gross undereporting of ADRs and because a definite causal association cannot be determined, this information cannot be used to estimate the incidence of adverse reactions.

ADRs are nevertheless invaluable as a source of potential new and undocumented signals.